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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/285,429	04/02/1999	BRET A. SHIRLEY	5784-9	3707

27476 7590 09/29/2005

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/285,429	SHIRLEY ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-34,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-34, 45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

2. The Request for Continued Examination (RCE) filed on August 5, 2005 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

3. Claims 21-34 and 45-46 are pending.

Applicants' response filed August 5, 2005 is acknowledged, and the response has been fully considered. Claim 21-34 and 45-46 are examined.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 21-34 and 45-46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over by Clark *et al.* (U. S. Patent 5,597,802, published January 28, 1997).

Clark *et al.* teach a composition comprising IGF-I, an osmolyte, a stabilizer and a buffer solution of about pH 5-5.5, and a formulation comprising mixing the IGF-I composition with a buffered solution comprising GH at pH 6.0, where the buffer may be any suitable buffer that is GRAS (generally regard as safe) and confers a pH of 5-6 on the GH+IGF-I formulation and a pH of about 5-5.5 on the IGF-I formulation, and the buffers include acetate, succinate, phosphate,

and citrate buffers (column 13, lines 16-24). The reference indicates a particular composition may comprises IGF-I and GH in a weight ratio of IGF-I: GH of between 2:1 and 100:1, 0.05-0.3 mM of osmolyte (e.g., sodium chloride, potassium chloride and mannitol), about 0.1-0.6 mg/ml of at least one stabilizer, about 1-5 mg/ml of a surfactant and about 5 to 100 mM of a buffer at pH 5-6 (column 12, lines 14-35; claims 21-30), and a broader pH range in terms of stability of both proteins is from about 5 to about 6 (column 14, lines 42-44). The reference also suggests that the composition may be administered parenterally, preferably by injection, and the formulation is sterile (column 5, lines 44-52; column 9, line 57-column 10, line 10; column 13, lines 38-41; claim 45), wherein IGF-I can be a recombinant human IGF-I (column 8, lines 46-50; claim 31); and the composition may contain 2-50 mg/ml of sodium chloride (corresponding to 34-855 mM) as osmolyte (also referred as isotonic modifier; column 12, lines 26-35; column 14, lines 12-23; claim 32 and 46). The reference also teaches the final preparation can be a stable liquid or lyophilized solid (column 13, lines 33-37; claims 33 and 34). Although the reference does not specifically provide an example of succinate buffer at a concentration of 10-40 mM for IGF-1-containing composition, the reference does suggest the use of a suitable buffer such as succinate from a group of acetate, succinate, phosphate and citrate buffers in preparing a composition comprising IGF-I and GH at pH 5-6, where a concentration of 5 to 100 mM buffer can be used, and it is known that succinate having pK2 of 5.64 is used to prepare a buffer in the pH range of 5.5-6.5, thus at the time of invention was made, it would have been obvious that one of ordinary skill in the art is motivated to prepare a pharmaceutical composition comprising IGF-I and GH at pH 6 using the succinate buffer as suggested by the reference, which results in the

claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Response to Arguments

Applicants indicate that the specification of instant application discloses pharmaceutical formulations that are buffered with succinate at the concentration ranges recited in these claims result in reduced pain on injection relative to those formulated with other buffers at similar concentrations; The '802 patent lists succinate as a member of a Markush grouping of GRAS buffers that can suitably be used to practice the '802 invention. However, the only disclosure of a buffer concentration within the '802 patent resides in the specification at column 12, lines 14-26, wherein a preferred composition comprises IGF-I and GH, an osmolyte, an inorganic salt and/or sugar alcohol, at least one stabilizer, a surfactant, and "about 5 to 100 mM of a buffer at about pH 5-6." Applicants indicate that the reference to succinate within the context of a list of GRAS buffers merely invites experimentation, and an invitation to experiment is not sufficient grounds to reject an invention as obvious; The '802 patent clearly teaches the advantages of formulating IGF-I with a sodium acetate buffer in the pH range of 5.0 to 5.5 (see column 14, lines 12-30 & 31-44). The '802 patent in fact teaches that the IGF-I formulation to be mixed with the GH solution preferably uses 50 mM sodium acetate to ensure that the final pH in the IGF-I+GH mixture will not vary significantly from pH 5.4 to maintain solubility of both proteins (column 14, lines 38-42). Further, the working examples (Examples V-XIV) in the '802 patent clearly teach away from Applicants' claimed invention, as they repeatedly describe the desirability of the increased potency and efficacy of IGF-I and/or IGF-I+GH compositions formulated with 50 mM sodium acetate buffer at a pH range of 5.0 to 5.5, and there is no motivation to modify this

reference to formulate IGF-I with a succinate buffer, particularly at pH 6.0, and particularly at the concentration ranges recited in Applicants' claimed invention. Given the laundry list of buffers generically disclosed for use in practicing the invention of the '802 patent, and the broad concentration range of buffer disclosed in the context of a preferred IGF+GH formulation, one of ordinary skill in the art would not have a reasonable expectation of success in selecting the concentration ranges of the succinate buffer utilized by Applicants to reduce pain upon injection (pages 2-6 of the response).

Applicants' response has been considered, however, the argument is not found persuasive because the '802 patent does suggest the use of succinate from a group of buffers containing a limited members (i.e., acetate, succinate, phosphate, and citrate) and the use of a concentration of 5 to 100 mM of buffer for preparing a pharmaceutical composition comprising IGF-I and GH at pH 5-6 (column 13, lines 16-24). Although the '802 patent indicates that the IGF-I formulation to be mixed with the GH solution preferably uses 50 mM sodium acetate to ensure that the final pH in the IGF-I+GH mixture will not vary significantly from pH 5.4 to maintain solubility of both proteins (column 14, lines 38-42), it also states that "a broader pH range in terms of stability of both proteins is from about 5 to about 6" (column 14, lines 42-44). Furthermore, it is known that succinate with pK2 of 5.64 is suitable for preparing a buffer in the pH range of 5.5-6.5 and with pK1 =4.21 is also suitable for preparing a buffer of pH 3.2-5.2. Therefore, although the reference cites IGF-I compositions are preferably formulated with sodium acetate buffer, it is obvious that acetate having pKa of 4.76 is preferred for a buffer of pH 3.6-5.6, but it is not suitable for a buffer at pH 6.0, where both IGF-I and GH are stable at this pH. Moreover, the preferable embodiment (i.e., acetate buffer, pH 5.5; Examples V-XIV) does not exclude other

embodiments (i.e., succinate, citrate, pH 6.0) in the genus. Regarding the concentration range of the buffer (5-100 mM) in such compositions being broad, such that one of ordinary skill in the art would not have a reasonable expectation of success in selecting the concentration ranges of the succinate buffer utilized by Applicants to reduce pain upon injection, the argument is not persuasive because this concentration range is commonly used for preparing buffers in a composition, where reducing pain during rejection is an issue. Therefore, it is obvious that one of ordinary skill in the art would prepare a pharmaceutical composition comprising IGF-I and GH at pH 5.0-6.0 using the succinate buffer at a concentration of 5 to 100 mM as suggested by the reference and the known pKa of succinate, which results in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusion

5. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
September 27, 2005